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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,493	11/21/2003	Arthur M. Krieg	C1039.70021US01	3218

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EXAMINER	
TUNGATURTHI, PARITHOSH K	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
02/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/719,493	KRIEG ET AL.	
	Examiner	Art Unit	
	Parithosh K. Tungaturthi	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-53,59-69,71-73 and 75-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-53,59-69,71-73 and 75-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/01/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/01/2007 has been entered.

2. Claims 1-41, 54-58, 70 and 74 have been cancelled.

Claims 79 and 80 have been added.

Claims 42 and 71 have been amended.

3. Claims 42-53, 59-69, 71-73 and 75-80 are under examination.

4. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

Rejections Withdrawn

5. The rejection of claims 56-58, 70 and 74 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter

which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn in view of the cancellation of claims.

Rejections Maintained

6. Claims 42-53, 59-69, 71-73, 75-79 and the newly added claims 79-80 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The applicants argue (pages 7-19 of the response filed on 11/01/2007) that the specification provides a representative species of CpG oligonucleotides as well as data demonstrating their immunostimulatory activity ... oligonucleotides containing an unmethylated CpG are effective in stimulating B-cell proliferation, IgM secretion, IL-6 production, induction of IL-12, induction of IFN-γ and induction of NK cell Stimulatory Activity ... oligonucleotides containing an unmethylated CpG dinucleotide produced an immune response that is consistent with the treatment of cancer ... at the time of filing the patent application, it was well known in the art that induction of IL-12, IFN-γ and IL-6 as well as NK cell activation was useful in the treatment of cancer ... the art cited by the examiner with respect to the lack of enablement rejection are post-filing references and the post-filing references can only be cited to establish what was known in the art at the time the patent application was filed ... the prior art as well as the post-filing art overall

are consisted with and support the use of CpG oligonucleotides in the treatment of cancer based on the data and descriptions in the patent applications as filed ... one of skill in the art would simply need to follow the guidance provided in the specification using a class of molecules which is commercially available or easily synthesized.

The above arguments are carefully considered but are not found persuasive. The specification discloses the immunostimulatory activity of oligonucleotides containing an unmethylated CpG dinucleotide. However, such disclosure does not enable a skilled artisan to treat cancer comprising administering oligonucleotides containing an unmethylated CpG dinucleotide. The state of the art is such that there is a high degree of unpredictability in the treatment of cancers comprising administering oligonucleotides containing an unmethylated CpG dinucleotide. The claims are drawn to a method of treatment of cancer comprising a huge genus of oligonucleotides containing an unmethylated CpG dinucleotide. In view of the unpredictability in the art, with regard to the treatment of cancers, one of ordinary skill in art would require an undue experimentation to practice the claimed method with all the oligonucleotides encompassed within the claims. Further, the claims require administering an effective amount of the oligonucleotides ranging from 8 to 100 nucleotides. Thus, the process of achieving a desirable effective amount for administration *in vivo* for each and every one of the oligonucleotides encompassed within the huge genus of oligonucleotides encompassed by the claims is a very lengthy and complicated process; because, the prior art recognizes that unlike the situation *in vitro*, a tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularisation, perfusion

and, thereby drug access to the tumor cells are not evenly distributed and this fact 'consists' an important source of heterogeneity in tumor response to drugs that does not exist *in vitro*. Therefore, prediction of drug effects in cancer patients based solely on *in vitro* data is not reliable and further evaluation in animal tumor systems is essential."

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

Supporting documents cannot be relied upon to correct the deficiencies of the specification by supplying the necessary and essential teachings, guidance, and exemplification that the specification lacks. MPEP 2164.05(a) states that if individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered. In *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993) an article published 5 years after the filing date of the application adequately supported the examiner's position that the physiological activity of certain viruses was sufficiently unpredictable so that a person skilled in the art would

not have believed that the success with one virus and one animal could be extrapolated successfully to all viruses with all living organisms. Hence, as stated in the previous office actions, the studies published well after the filing date of the instant application clearly recognize the obstacles in treating cancers comprising oligonucleotides containing an unmethylated CpG dinucleotide and address the unpredictability. Particularly, Krieg et al in 2006 teach that it will be necessary to use combinations of synergistic therapies to achieve the full clinical potential of this approach; and that further studies into the effects of various chemotherapy regimes on immune function might make it possible to design combination therapies that will predictably provide greater clinical benefit to patients, indicating that the method of treating cancers comprising oligonucleotides containing an unmethylated CpG dinucleotide is still not completely resolved and requires further analysis and experimentation. The post-filing art cited by the applicant with regard to the clinical trials is not found persuasive because the references are directed towards viral studies, and further the art demonstrates T cells responses and immunogenicity of only one CpG dinucleotide. Hence, such results cannot be extrapolated to the treatment of any cancer with a huge genus of CpG dinucleotides encompassed within the claims.

Further, with regard to CpG in the treatment of cancers, Weiner J (Leukocyte Biology, 68(4):455-463, 2000) indicates that there is therapeutic potential in cancer treatment for CpG as an immune adjuvant (Table 1) and that there are a number of scenarios where CpG could be used as a component of cancer immunotherapy, each of these areas is under intensive investigation (p. 458, col. 1). Studies in a tumor model

(38C13 murine lymphoma) indicate that CpG was just as effective as CFA at inducing an antigen-specific antibody response (p. 458, col. 2). Weiner teaches that "[P]reliminary studies suggest CpG ODN can be effective in a variety of scenarios when used alone or in combination with other agents. Despite this promise we still do not understand the molecular mechanisms responsible for the immunostimulatory effects of CpG ODN. All CpG ODN are not alike, and more needs to be learned about the heterogeneous responses that occur based on host organism, cell subset, or CpG ODN sequence. Most importantly, we have not yet explored their clinical effects. Further work with CpG ODN in both the laboratory and the clinic is needed before we can know their true promise as investigational immunological and therapeutic agents." (p. 461, col. 1) Krieg et al (Nature, 374:546-549, 1995) teaches that CpG has NK-stimulating properties and suggest that it can be used in immunotherapy of tumors, yet Krieg et al also indicates that many or even most types of tumors are relatively resistant to NK-mediated lysis (p. 117, col. 2). Ballas et al (The Journal of Immunology, 167:4878-4886, 2001) teaches that the selection of optimal CpG ODN for cancer immunotherapy depends upon a careful analysis of the cellular specificities of various CpG motifs and an understanding of the cellular mechanisms responsible for the antitumor activity in a particular tumor (abstract). Ballas et al teaches that a single CpG ODN cannot be used to treat all cancers and tumors. Although several CpG ODN were active as sole immunotherapeutic agents in two tumor models, different motifs were optimal in each model. CpG ODN 1585 was optimal against B16 melanoma and its effects were dependent on NK cells. CpG ODN 1826 was optimal in a lymphoma model and its

effects appeared to require NK (early) and T cells (late). These results illustrate that the potent distinct CpG motifs can be custom-tailored for each desired immune effect (p. 4878, col. 2; see also p. 4885, col. 1). Agrawal et al (TRENDS in Molecular Medicine, 2002, 8/3:114-120) also teaches that different effects are observed with different CpG ODNs.

The description and the data found in the specification is not sufficient, because the specification does not teach those skilled in the art how to make and use the full scope of the claimed invention, which is the treatment of cancer comprising administering CpG immunostimulatory oligonucleotides comprising 8 to 100 nucleotides in length, without undue experimentation. The examples in the specification show that unmethylated CpG are effective at stimulating B-cell proliferation, cytokine secretion for example; however, based on the undue experimentation necessary in understanding the treatment of cancer comprising CpG molecules as taught by the prior art, the amount of additional experimentation is deemed to be undue. In order to practice the claimed invention with a reasonable expectation of success, one of skill in the art would have to show evidence overcoming art recognized problems that the broadly claimed CpG-containing oligonulceotides would not work for treating any cancer.

Thus, taken collectively, there is a preponderance of factual evidence of record that the showing provided in the supporting disclosure would not enable the skilled artisan to practice the claimed invention without undue experimentation, as required under the provisions of 35 U.S.C. § 112, first paragraph.

While it is agreed that human clinical data is not needed and that the office does not require the clinical success of a drug, it should be noted that PTO requires the enablement of the claimed invention. In the instant case, the claims are drawn to a method of treatment of cancer. Based on the unpredictability that exists in treatment of cancers, it is necessary to show the correlation of the working examples with the claimed invention. The studies as disclosed in the specification do not support this theory because neither the specification nor prior art describe a direct correlation between induction of cytokines and treatment of cancer. Further, the prior art as cited before clearly shows the unpredictability that exists in the treatment of cancer. In addition, the specification only shows the induction of cytokines in vitro and the extrapolation of such results into treatment of cancer is merely a contemplation.

Thus, in conclusion, the applicant is reminded that the high degree of unpredictability recognized in the art, particularly the required characteristics of the immunostimulatory oligonucleotide in order to be an effective in vivo immunostimulatory oligonucleotide; the breadth of the claims as mentioned above; the limited number of working examples and guidance in the specification; and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed vaccine composition is undue.

The references clearly point towards the undue experimentation needed in practicing the treatment of cancers comprising CpG molecules. Thus, The instant application gives no data relevant to the use of the nucleic acids mentioned in the claims in any in vivo method to control or affect any of the conditions mentioned in the

claims. One skill in the art would be compelled to perform undue experimentation in order to practice the claimed invention because of the large number of variables connected with the use of such nucleic acids. For example, the instant application does not give guidance as to the type of administration, the times or frequencies of administration, or the dosages required to obtain desired effects.

Conclusion

7. No claims are allowed

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

9. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
Parithosh K. Tungaturthi
Ph: (571) 272-8789

DAVID J. BLANCHARD
~~PATENT~~ EXAMINER
PRIMARY